REMARKS

Claims 1-3, 5-9 and 11-18 are pending. Claims 11-14 and 18 have been withdrawn from consideration. Claims 1-3, 5-9 and 15-17 have been rejected. Claims 1, 2, 7, 11, 12 and 16 have been amended. Claims 9, 11 and 18 have been canceled. Claims 1-3, 5-8 and 12-17 remain in the case.

Claims 11-14 and 18 have been withdrawn from consideration. Claims 11-14 are a process of using the vaccine of claim 1. A notice published in the *Official Gazette* on March 26, 1996, establishes a new procedure for rejoinder of process claims in a case where product claims are allowable, in light of *In re Ochiai*, 37 USPQ2d 1127 (Fed. Cir. 1995) and *In re Brouwer*, 37 USPQ2d 1663 (Fed. Cir. 1996). The procedure is outlined in "Training Materials for Treatment of Product and Process Claims in Light of *In re Brouwer* and *In re Ochiai*" (Office of Patent Policy Dissemination, Patent Academy). If an applicant elects claims directed to a product, and the product is subsequently found allowable, withdrawn process claims which depend from or otherwise include all the limitations of the allowable product will be rejoined and examined by the examiner. Claim 11 has been amended to include all the limitations of the vaccine of claim 1. Once the vaccine of claim 1 is found allowable in this case, claims 11-14, to a process of using the vaccine of claim 1 should be rejoined and examined. It is believed appropriate to raise this issue at this juncture since (1) applicants' initial response to restriction was made before the aforementioned OG Notice and guidelines were promulgated, (2) process claims have been pending continuously in the case.

Claim 1 is rejected under the first paragraph of §112, "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." A recitation in claim 1, to the effect that the purified, detoxified LPS endotoxin is "devoid of O-oligosaccharide side chains," has been eliminated, not because it was unsupported but because it was redundant. That is, the recited aspect is an inherent feature of endotoxin "derived from *E. coli* J5 strain." *E. coli* J5 strain lacks epimerase that prevents the attachment of O-oligosaccharide side chains to core polysaccharide; accordingly, it produces endotoxin that is devoid of such side chains. See, for example, Ziegler *et al.* (1982) at page 1225, right-hand column. The recitation that the vaccine is not bactericidal also has been deleted.

The recitation of "detoxified" OMP, which was inadvertently inserted in claim 1 in applicants' previous response, no longer appears in claim 1. However, such a recitation would have been supported. The specification describes that "the outer membrane protein therefrom (hereinafter "GBOMP") is prepared as described in Zollinger *et al.*, *J. Clin. Invest.* 63:836 (1979), and U.S. patent No. 4,707,543 (1987), the contents of which are incorporated herein by reference" - emphasis added. Column 10 of Zollinger teaches that "the proteins are further purified to remove lipopolysaccharides." Native lipopolysaccharide is toxic, hence Zollinger removes it from the outer membrane proteins, thereby "detoxifying" the outer membrane proteins. Zollinger then complexes the

outer membrane protein with detoxified native lipopolysaccharides. Accordingly, a recitation of "detoxified" OMP would be supported by reference to Zollinger.

Claims 1-3, 5, and 15-17 stand rejected under the first paragraph of §112. Claim 1 has been amended to remove the recitation of "passive" immunization, which already is covered by claims 11-14.

Claims 1-3, 5-9 and 15-17 stand rejected under the first paragraph of §112 for failing "to enable one skilled in the art to make and/or use the invention." At the outset, it is noted that much of the discussion relating to "enablement" actually is a §101 utility-like argument made under the guise of §112, which is deemed to be improper in light of both the PTO's utility and enablement guidelines. The rejection employs lack of utility language, with the examiner asserting that "the specification fails to provide evidence correlating the data disclosed from the rabbit and rat models with the scope of the claimed invention, such that the evidence disclosed is predictive of reactivity in humans."

According to the MPEP §2164.07(a)(1), "a 35 U.S.C. 112, first paragraph, rejection [for lack of utility] should not be imposed or maintained unless an appropriate basis exists for imposing a rejection under 35 U.S.C. 101. In other words, Office personnel should not impose a 35 U.S.C. 112, first paragraph, rejection grounded on a 'lack of utility' basis unless a 35 U.S.C. 101 rejection is proper. In particular, the factual showing needed to impose a rejection under 35 U.S.C. 101 must be provided if

a 35 U.S.C. 112, first paragraph, is to be imposed on 'lack of utility' grounds" (citing MPEP §706.03(a)(1) and §2107-§2107.02). The examiner here has not provided the factual showing necessary to support her doubts about the value of the neutropenic rat as a model, in spite of the fact that an examiner has the initial burden to show that one of ordinary skill in the art reasonably would doubt the asserted utility of the neutropenic rat model. MPEP §2164.07(a)(2):

The cited portion of the MPEP cites *In re Brana*, which holds that where the skilled artisan would have no basis reasonably to doubt an asserted utility there can be no rejection under the first paragraph of 35 U.S.C. §112. The *Brana* standard enunciated by the Federal Circuit dovetails closely with the PTO guidelines on utility. In the guidelines, the Commissioner has reasoned that a claimed invention only violates 35 U.S.C. §101 if it is **"wholly inoperative."** If an asserted utility is credible, then there can be no rejection based upon 35 U.S.C. §101. In view of *Brana*, the same holds true for 35 U.S.C. §112.

While applicants should not be required to substantiate their presumptively correct disclosure, they have provided a declaration of Dr. Steven Opal which does provide evidence of the correlation sought by the examiner. An unsigned copy of this declaration was submitted previously, and it has not been considered by the examiner because of its lack of signature. Forwarded with this response is a signed copy of Dr. Opal's declaration, for consideration and entry.

Dr. Opal, a Professor of Medicine at Brown University, is considered a foremost expert in this field, and has extensive experience with the neutropenic rat model for heterologous Gram-negative bacterial infection. In fact, Dr. Opal was a member of the group at NIH that wrote the guidelines reviewing animal models of sepsis. While this group recognized that all animal models have limitations, it still confirmed their value in preclinical studies.

Dr. Opal attests that there is no animal model for sepsis other than the neutropenic rat model used by applicants which provides such extensive correlations with human clinical trials. Dr. Opal provides four specific examples of antibodies (HA-IA mAb, anti-lipid A antibody E5, BPI and IL-lra) for which there is a high correlation between the results with the neutropenic rat and the results with clinical trials with humans. The established correlation between neutropenic rat and human with respect to these antibodies for treatment of lipopolysaccharide endotoxin-mediated sepsis definitively addresses the examiner's concern that "no convincing evidence has been provided indicating that the neutropenic rat or the rabbit animal model are predictive of successful treatment in humans against infection by heterologous Gram negative bacteria or against lipopolysaccharide endotoxin-mediated diseases."

Further evidence that the neutropenic rat is an art-accepted model for the present purposes is provided by Dr. Opal's description of requests that he has received from pharmaceutical companies to use the neutropenic rat model to test their candidate vaccines. These requests

are further evidence that the companies consider the neutropenic rat model to be a predictive model.

The examiner also questions the "rabbit model." However, the present specification does not described the use of rabbits as a test animal for the determination of the immunotherapeutic efficacy of the inventive purified, detoxified LPS-OMP complex. Rather, the rabbit is used merely to determine the immunogenicity of the J5 LPS-GBOMP non-covalent complex vaccine (p.6, lines 16-17 and Example 7) and to determine pyrogenicity of the aforementioned complex vaccine (Example 5). It is critical to understand that neither of these uses of the rabbit involves testing the efficacy of the complex vaccines of the invention, that is, immunotherapy against Gram-negative bacteria or against LPS endotoxin-mediated pathology.

Finally, in a declaration appended to this response, Dr. Cross attests that a clinical protocol for Phase I trials in humans has been written, to assess the safety of the present vaccine for immunizing subjects against infection by heterologous Gram-negative bacteria or against lipopolysaccharide (LPS) endotoxin-mediated pathology. This protocol, which presented results with the neutropenic rat model, has been approved by (1) the Walter Reed Army Institute of Research (WRAIR) Scientific Review Committee; (2) the WRAIR Institutional Review Board (IRB); and (3) the Surgeon General's Human Subjects Research Review Board, pending only the formality of credentialing of Dr. Cross at WRAIR so that he can act as principal investigator. The imprimatur of these review boards, embodied in their approval of the present vaccine for clinical trials, is commanding evidence with respect

to whether data from neutropenic rats is enabling in the present case.

Dr. Cross attests that his co-inventor Dr. Bhattacharjee consulted with Dr. Richman at the FDA about the specifics of the protocol, who suggested only minor modifications to the Phase I trial. These modifications were incorporated in the protocol, which is in the approval process. As noted in MPEP §2107.02, "before a drug can enter human clinical trials, the sponsor, often the applicant, must provide a convincing rationale to those especially skill in the art (*e.g.*, the Food and Drug Administration) that the investigation may be successful" and "in such a situation, experts at the FDA have assessed the rationale for the drug or research study upon which an asserted utility is based and found it satisfactory. Thus, in challenging utility, Office personnel must be able to carry their burden that there is no sound rationale for the asserted utility even though experts designated by Congress to decide the issue have come to an opposite conclusion." The fact that the FDA suggested only minor modifications to applicants' protocol indicates that it found the rationale for the trial, *i.e.*, data from neutropenic rats, to be based on sound scientific principles.

Thus, while under no obligation to do so, applicants have provided extensive evidence that the neutropenic rat model used in the examples in the specification is reasonably predictive of efficacy in humans. Reconsideration and withdrawal of the rejection for lack of enablement is respectfully requested.

A rejection under §102(b) based on Zollinger *et al.* has been withdrawn, and only a §103(a) rejection based on that reference remains. Zollinger describes a process for preparing detoxified polysaccharide-outer membrane protein complexes. The polysaccharide may be capsular polysaccharide or detoxified lipopolysaccharide, although only capsular polysaccharides are exemplified (complexes with lipopolysaccharides are prepared in Example 3, but never tested for bactericidal antibody response).

The purpose of the polysaccharide in Zollinger, whether capsular polysaccharide or lipopolysaccharide, is to solubilize the outer membrane proteins. Thus, Zollinger speaks of "outer membrane proteins...solubilized by the tetravalent mixture of A, C, Y, and W135 polysaccharides" (col. 2, lines 7-9), and describes that "the detoxified [lipopolysaccharide] was shown to retain its ability to bind to and solubilize outer membrane proteins" (col. 8, lines 66-68); and "sonication is often essential to facilitate the protein-lipopolysaccharide interaction and solubilize the protein" (col. 9, lines 13-15; emphasis added in each case). For the purpose of solubilization, either detoxified lipopolysaccharide or capsular polysaccharide can be used, and Zollinger teaches that all capsular polysaccharides and lipopolysaccharides are equivalent for this purpose (col. 9, lines 45-48).

Zollinger does not teach or suggest a vaccine comprising LPS endotoxin from the *E. coli* J5 mutant. As noted above, this mutant strain produces endotoxin that lacks O-oligosaccharide side chains. Since Zollinger does not specifically teach the use of endotoxin derived from J5 mutant, the basis for the present rejection must be

that it would have been obvious to substitute endotoxin from this mutant for capsular polysaccharides or for lipopolysaccharide purified from a serogroup B case strain because equivalent results would be achieved. The premise on which the rejection is based is that all lipopolysaccharides behave equivalently in combination with outer membrane protein.

In his declaration, Dr. Cross discusses studies which show that combinations of OMP derived from *N. meningitidis* and purified, detoxified LPS endotoxin derived from *E. coli* strain J5 provide unexpectedly superior protection against Gram-negative sepsis as compared to combinations of OMP with purified, detoxified LPS endotoxins from other strains of bacteria, including other strains of *E. coli*. Vaccination with *Brucella*-OMP resulted in 0% protection against heterologous (EC018), as would be expected for heterologous challenge. On the other hand, vaccination with J5-OMP led to 90% survival in the face of heterologous challenge, a totally unexpected result. The 90% survival rate was 50% greater than a 60% survival rate following homologous challenge among mice vaccinated with EC018-OMP (a complex of OMP with another strain of *E. coli*). It is very surprising that J5-OMP vaccine provided a higher level of protection against a heterologous challenge than EC018-OMP could provide against a homologous challenge. The results reported in the Cross declaration could not have been predicted based on Zollinger, which teaches that all capsular polysaccharides and lipopolysaccharides behave equivalently in combination with an outer membrane protein for the purpose of solubilization as disclosed in Zollinger. The data in the Cross declaration shows an

unexpected result for complexes of OMP and J5. In view of the foregoing, reconsideration and withdrawal of the rejection under §103(a) based on Zollinger is respectfully requested.

The data in the Cross declaration is consistent with that in Table 1 and Figure 1 of Bhattacharjee *et al.*, *Journal of Infectious Diseases* **173**:1157-1163 (1996), a copy of which is appended. The GBOMP in the article comprises OMP with capsular polysaccharide and with LPS from *N. meningitidis*. This composition did not elicit J5 antibody production, and provided 0% protection against infection by heterologous Gram-negative bacteria or against lipopolysaccharide (LPS) endotoxin-mediated pathology.

In view of the amendments to the claims and the foregoing remarks, it is believed that all claims are in condition for allowance. Reconsideration of all rejections and a notice of allowance are respectfully

requested. Should there be any questions regarding this application, Examiner Loring is invited to contact the undersigned attorney at the phone number listed below.

Respectfully submitted,

June 19, 1998
Date

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The Commissioner is hereby authorized to charge any fee required by the filing of this response to Deposit Account No. 19-0741.